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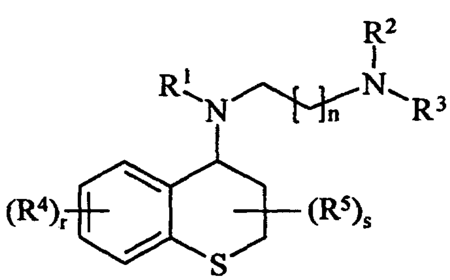

(I)

(57) Abstract: Methods for the use of compounds of formula (I) for treatment of neurological disorders, wherein n, r and s are as defined in the specification and R^1, R^2, R^3, R^4 and R^5 are various substituents, also as defined in the specification, such compounds and pharmaceutical compositions containing such compounds.

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THIOCHROMAN DERIVATIVES AGAINST NEUROLOGICAL DISORDERS

The present invention relates to chemical compounds, in particular thiochromans, to processes for their preparation and to chemical intermediates useful in such processes. The present invention further relates to thiochromans, to pharmaceutical compositions containing them and to their use in methods of therapeutic treatment of animals including man, in particular in the treatment of neurological disorders.

Neurological disorders, for which the present compounds are useful, include stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. The compounds useful in the present invention act by selectively binding to the [^{3}H]-emopamil binding site. Compounds with selective action at the [^{3}H]-emopamil binding site exhibit fewer associated side effects such as hypotension seen with emopamil or behavioural manifestations seen with ifenprodil.

Background

Emopamil has classically been thought of as a neuroprotective agent whose efficacy is most likely derived from actions at either voltage-sensitive calcium channels (VSCC) or 5-HT_2 receptors. An apparent paradox to this logic is that verapamil, although chemically and pharmacologically very similar to emopamil, is not neuroprotective. While the lack of neuroprotective efficacy by verapamil was initially explained by lack of CNS penetration, recent studies suggest other factors may be involved (Keith et al., Br. J. Pharmacol. 113: 379-384, 1994).

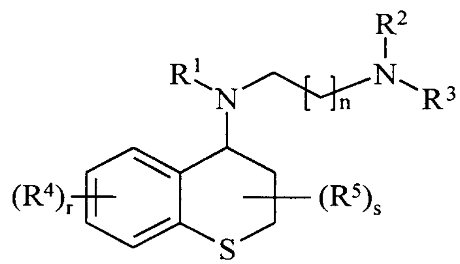
[^{3}H]-Emopamil binding defines a unique high affinity site that is not related to VSCC, is found in the brain, but is most prevalent in the liver (Moebius et al., Mol. Pharmacol. 43: 139-148, 1993). Moebius et al. have termed this the "anti-ischaemic" binding site on the basis of high affinity displacement by several chemically disparate neuroprotective agents. In liver, the [^{3}H]-emopamil binding site is localised to the endoplasmic reticulum.

Neuroprotective compounds are known, for example emopamil and ifenprodil, that exhibit high affinity for the [^{3}H]-emopamil binding site. However these are not selective inhibitors and exhibit activity either at neuronal VSCC, the polyamine site of the NMDA receptor (N-Methyl-D-aspartate) and/or the sigma-1 binding site.

Summary of the Invention

In one aspect of the present invention a new method for using compounds having selective action at the [^{3}H]-emopamil binding site and that are neuroprotective without acting directly at either VSCC or NMDA receptors is disclosed.

Compounds of the invention that have selective action at the [^{3}H]-emopamil binding site are compounds of formula (I):



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl;

R^4 is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the values of R^4 may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the values of R^5 may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In another aspect of the present invention, new pharmaceutical compositions containing compounds of formula (I), or *in vivo*-hydrolysable esters, amides or carbamates thereof, together with a pharmaceutically-acceptable carrier such as an excipient, diluent or stabilizer or combinations thereof as further defined herein are disclosed.

In a further aspect of the present invention, the use of a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in the manufacture of a medicament for use in the inhibition of the [^{3}H]-emopamil binding site in a warm-blooded animal is disclosed.

In yet a further aspect of the present invention, novel compounds are disclosed which are compounds of formula (I) with a proviso wherein in such compounds:

if R^1 is hydrogen, R^2 and R^3 and the nitrogen to which they are attached in combination form a morpholine or piperidine ring, n is 1 and s is 0, then r is not 0, or R^4 is not a 5-linked ethoxy moiety.

Detailed Description of the Invention

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. A similar convention applies to "alkenyl", "alkynyl" and other radicals, for example "phenylC_{1-6}alkyl" includes 2-phenylethyl, 2-phenylpropyl and 3-phenylpropyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

The term aryl refers to an unsaturated carbon ring. Preferably aryl is phenyl, naphthyl or biphenyl. More preferably aryl is phenyl.

The term "heteroaryl" or "heteroaryl ring" refers to, unless otherwise further specified, a monocyclic-, bicyclic- or tricyclic- 5- to 14-membered ring that is unsaturated or partially unsaturated, with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring nitrogen atom may be optionally oxidised to form the N-oxide. Examples of such heteroaryls include thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, pyridyl-*N*-oxide, oxopyridyl, oxoquinolyl, pyrimidinyl, pyrazinyl, oxopyrazinyl, pyridazinyl, indolinyl, benzofuranyl, benzimidazolyl, benzothiazolyl, quinolyl, isoquinolinyl, quinazolinyl, xanthenyl, quinoxalinyl, indazolyl, benzofuranyl and cinnolinolyl.

The term "heterocyclyl" or "heterocyclic ring" refers to, unless otherwise further specified, a mono- or bicyclic- 5- to 14-membered ring, that is totally saturated, with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Examples of such heterocyclyls include morpholinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl and quinuclidinyl.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

In the present invention, examples of C_{1-6}alkyl include C_{1-4}alkyl such as methyl, ethyl, isopropyl and *t*-butyl;

examples of phenylC_{1-6}alkyl include phenylC_{2-6}alkyl such as phenylC_{1-4}alkyl such as phenylC_{2-4}alkyl such as benzyl, phenylethyl and phenylpropyl;
examples of C_{1-6}alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl;
examples of C_{1-6}alkoxy include methoxy, ethoxy and propoxy;
examples of C_{1-6}alkanoylamino include formamido, acetamido and propionylamino;
examples of C_{1-6}alkylS(O)$_a$ where a is 0, 1 or 2 include C_{1-6}alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl;
examples of C_{1-6}alkylsulphonyl include mesyl and ethylsulphonyl;
examples of C_{1-6}alkanoyl include propionyl and acetyl;
examples of *N*-C_{1-6}alkylamino include *N*-methylamino and *N*-ethylamino;
examples of *N*,*N*-(C_{1-6}alkyl)$_2$amino include *N*,*N*-dimethylamino, *N*,*N*-diethylamino and *N*-ethyl-*N*-methylamino;
examples of C_{3-12}cycloalkyl include cyclopropyl and cyclohexyl;
examples of C_{3-12}cycloalkyl fused to a benzene ring are 1,2,3,4-tetrahydronaphthyl and 2,3-dihydroindenyl;
examples of C_{2-6}alkenyl include vinyl, allyl and 1-propenyl;
examples of C_{2-6}alkynyl include ethynyl, 1-propynyl and 2-propynyl;
examples of haloC_{2-6}alkyl include 2-chloroethyl and 2-bromopropyl;
examples of *N*-(C_{1-6}alkyl)sulphamoyl include *N*-methylsulphamoyl and *N*-ethylsulphamoyl;
examples of *N*,*N*-(C_{1-6}alkyl)$_2$sulphamoyl include *N*,*N*-dimethylsulphamoyl and *N*-methyl-*N*-ethylsulphamoyl;
examples of *N*-(C_{1-6}alkyl)carbamoyl include *N*-methylcarbamoyl and *N*-ethylcarbamoyl;
examples of *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl include *N*,*N*-dimethylcarbamoyl and *N*-methyl-*N*-ethylcarbamoyl, and
examples of C_{1-6}alkanoyloxy include propionyloxy, acetyloxy and formyloxy.

Preferably R^1 is hydrogen, C_{1-6}alkyl or C_{2-6}alkenyl.

More preferably R^1 is hydrogen, C_{1-4}alkyl or C_{2-4}alkenyl.

Particularly R^1 is hydrogen, methyl, ethyl or allyl.

More particularly R^1 is hydrogen, methyl or ethyl.

In a particularly preferred aspect R^1 is methyl.

In one aspect of the invention, preferably R^2 and R^3 are independently selected from hydrogen, optionally substituted C_{1-6}alkyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring wherein said optional substituents are chosen from one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl or heterocycle may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl.

In another aspect of the invention preferably R^2 and R^3 and the nitrogen atom to which they are attached in combination form a ring selected from 1,2,3,4-tetrahydroisoquinolinyl, morpholinyl, piperidinyl, pyrrolidinyl, homopiperidinyl and wherein said ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl.

In a further aspect of the invention, preferably R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl; or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring wherein a heterocyclic ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl.

More preferably R^2 and R^3 are independently selected from hydrogen, methyl, ethyl, isopropyl, phenyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl, piperidin-1-yl, 4-methylpiperazin-1-yl, morpholino or 1,2,3,4-tetrahydroisoquinol-2-yl ring.

Particularly R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a piperidin-1-yl, morpholino, 4-methylpiperazin-1-yl, or 1,2,3,4-tetrahydroisoquinol-2-yl ring.

More particularly R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a piperidin-1-yl, morpholino or 1,2,3,4-tetrahydroisoquinol-2-yl ring.

Preferably r is 0.

Preferably s is 0.

In one aspect of the invention preferably n is 1.

In another aspect of the invention preferably n is 2.

Therefore in a preferred aspect of the invention there is provided an compound of formula (I) as depicted above wherein:

R^1 is hydrogen, C_{1-6}alkyl or C_{2-6}alkenyl;

R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring wherein a heterocyclic ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl;

r is 0;

s is 0; and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a more preferred aspect of the invention there is provided a compound of the formula (I) as depicted above wherein:

R^1 is hydrogen, methyl, ethyl or allyl;

R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a piperidin-1-yl, morpholino, 4-methylpiperazin-1-yl, or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

r is 0;

s is 0; and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a particular aspect of the invention there is provided a compound of formula (I) as depicted above wherein:

R^1 is methyl;

R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen to which they are attached in combination form a piperidin-1-yl, morpholino or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

r is 0;

s is 0; and

n is 1 or 2;

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

Preferred compounds of the invention are those of Examples.

A preferred aspect of the invention relates to any one of the Examples.

Preferred aspects of the invention relate to a compound or a pharmaceutically-acceptable salt thereof.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N*,*N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is a sodium salt.

The compounds of formula (I) possess a chiral centre at the 4-position of the thiochroman ring. Certain compounds of formula (I) may also have other chiral centres, for example certain of the values of R^2, R^3, R^4, R^5 and certain of the optional substituents may

possess chiral centres. It is to be understood that the invention encompasses all such optical isomers and diasteroisomers of compounds of formula (I) that inhibit the [^{3}H]-emopamil binding site.

The invention further relates to all tautomeric forms of the compounds of formula (I).

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated and unsolvated forms.

In vivo-hydrolysable esters, amides and carbamates are compounds that hydrolyse in the human body to produce the parent compound. Such esters, amides and carbamates can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo*-hydrolysable amides and carbamates include N-carbomethoxy and N-acetyl.

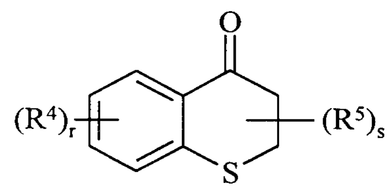
An *in vivo*-hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo*-hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo*-hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

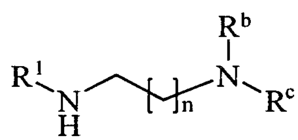
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof which process (wherein R^1, R^2, R^3, R^4, R^5, n, r and s are, unless otherwise specified, as defined in formula (I)) comprises of:

a) reacting a ketone of formula (II):



(II)

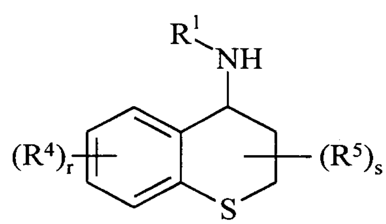
with an amine of formula (III):



(III);

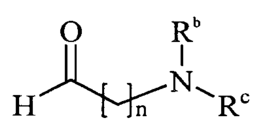
wherein R^b and R^c are R^2 and R^3 respectively, unless the value of R^2 and/or R^3 is hydrogen, in which case the appropriate R^b and/or R^c is a suitable amino protecting group such as those defined below; or

b) reacting an amine of formula (IV):



(IV)

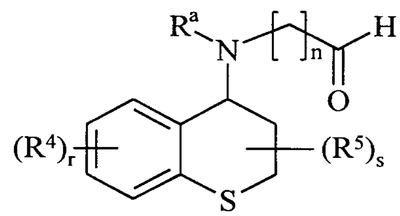
with an aldehyde of formula (V):



(V)

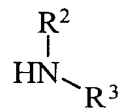
wherein R^b and R^c are as defined above; or

c) reacting an aldehyde of formula (VI):



(VI)

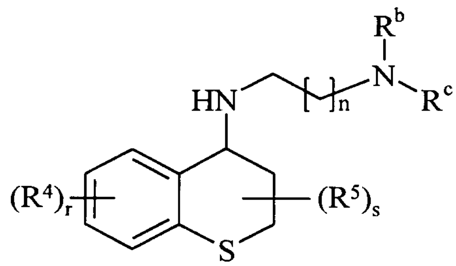
with an amine of formula:



(VII)

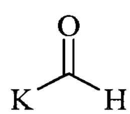
wherein R^a is R^1 unless the value of R^1 is hydrogen, in which case R^a is a suitable amino protecting group such as those defined below; or

d) if R^1 is C_{1-6}alkyl, reacting a compound of formula (VIII):



(VIII)

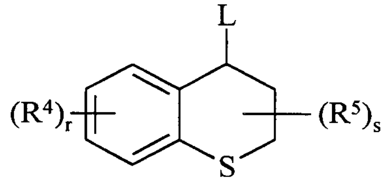
wherein R^b and R^c are as defined above, with a compound of formula (IX);



(IX)

wherein K is hydrogen or C_{1-5}alkyl; or

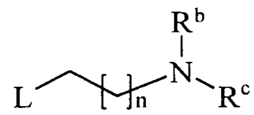
e) reacting a compound of formula (X):



(X)

wherein L is a suitable displaceable group, with an amine of formula (III); or

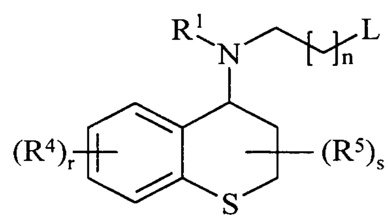
f) reacting an amine of formula (IV) with a compound of formula (XI):



(XI)

wherein L is a suitable displaceable group and R^b and R^c are as defined above; or

g) reacting a compound of formula (XII):



(XII)

wherein L is a suitable displaceable group, with an amine of formula (VII); or

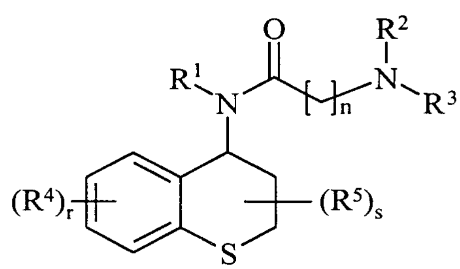
h) if R^1 is not hydrogen, reacting a compound of formula (VIII) with a compound of formula (XIII):

R^1-L

(XIII)

wherein L is a suitable displaceable group; or

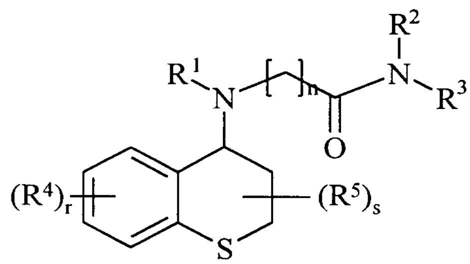
i) reducing a compound of formula (XIV):



(XIV)

or

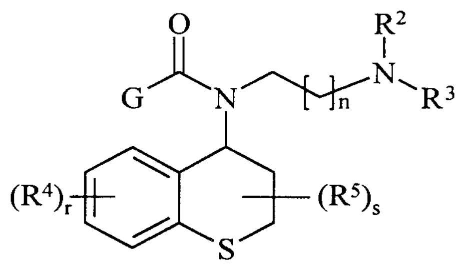
j) reducing a compound of formula (XV):



(XV)

or

k) if R^1 is not hydrogen, reducing a compound of formula (XVI):



(XVI)

wherein:

1) for preparing a compound wherein R^1 is methyl, G is a suitable displaceable group; or

2) for preparing a compound wherein R^1 is C_{2-6}alkyl, G is C_{1-5}alkyl; or

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups; or

iii) forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

When G is a suitable displaceable group, suitable values for G are C_{1-6}alkoxy, for example methoxy or ethoxy.

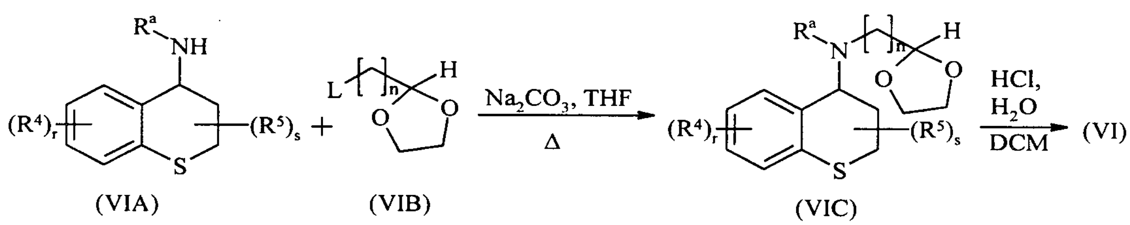
Specific reaction conditions for the reactions a), b), c) and d), above, are as follows.

Ketones or aldehydes may be reacted with amines under standard reductive amination conditions. Imine formation may optionally be assisted with a Lewis acid for example titanium tetrachloride, in an inert solvent for example toluene. The reduction may

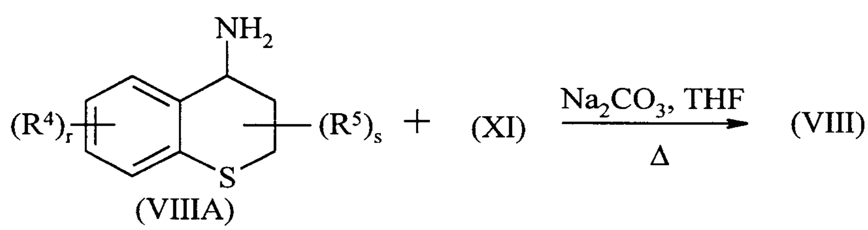
occur for example in the presence of a reducing agent such as hydrogen and a hydrogenation catalyst (for example palladium on carbon), or zinc and hydrochloric acid, or sodium cyanoborohydride, or sodium triacetoxyborohydride, or sodium borohydride, iron pentacarbonyl and alcoholic potassium hydroxide, or borane and pyridine or formic acid. The reaction is preferable carried out in the presence of a suitable solvent such as an alcohol, for example methanol or ethanol, and at a temperature in the range of 0-50 °C, preferably at or near room temperature.

Compounds of formula (II), (III), (IV), (V), (VII) and (IX) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Compounds of formula (VI) may be prepared according to the following scheme:



Compounds of formula (VIII) may be prepared according to the following scheme:



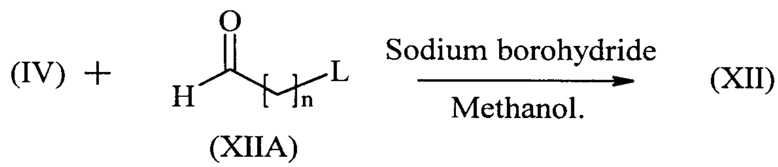
Compounds of formula (VIA), (VIB) and (VIIIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Specific reaction conditions for the reactions e), f), g) and h), above are as follows:

Amines and compounds with suitable leaving groups are reacted together under standard alkylation conditions. For example in the presence of a base, such as an inorganic base for example sodium carbonate or sodium hydroxide, or an organic base for example triethylamine, or in the presence of excess amine, in the presence of an inert solvent for example tetrahydrofuran or toluene and at a temperature in the range of 50-120 °C, preferably at or near reflux.

Compounds of formula (X), (XI) and (XIII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Compounds of formula (XII) may be prepared according to the following scheme.

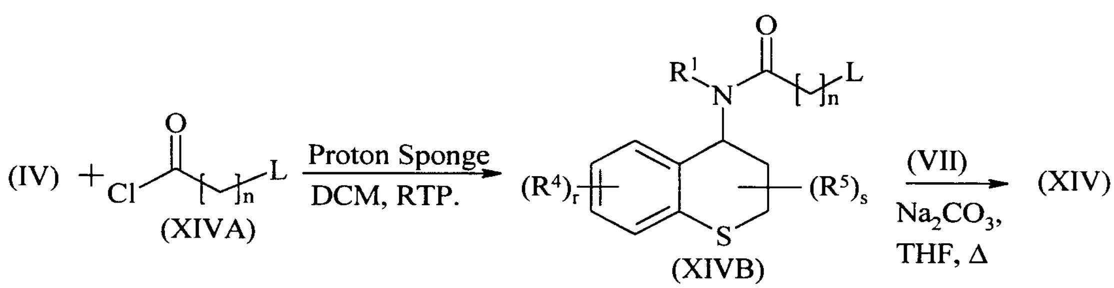


Compounds of formula (XIIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

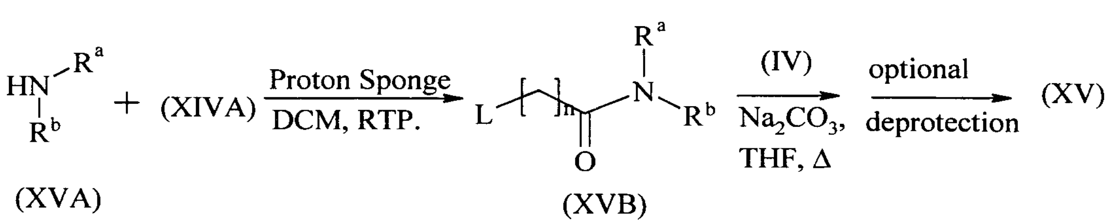
Specific reaction conditions for the reactions i), j) and k), above, are as follows:

Compounds of formula (XIV), (XV) and (XVI) are reduced under standard reduction conditions for reducing an amide to an amine. For example, in the presence of a reducing agent such as borane, borane methyl sulphide complex, sodium borohydride or lithium aluminium hydride, in an inert solvent such as toluene or tetrahydrofuran, and at a temperature in the range of 0-120 °C, preferably at or near reflux.

Compounds of formula (XIV) may be prepared according to the following scheme:

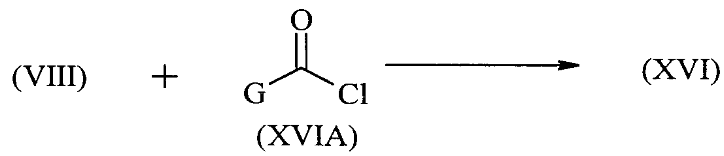


Compounds of formula (XV) may be prepared according to the following scheme:



wherein R^a, R^b and L are as hereinbefore defined.

Compounds of formula (XVI) may be prepared according to the following schemes:



Compounds of formula (XIVA) and (XVIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

When an optically active form of a compound of the formula (I) is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure.

An example of converting one compound of formula (I) into another compound of formula (I) is the conversion of R^1, R^2 or R^3 when they are hydrogen to a different R^1, R^2, or R^3. For example an alkyl group could be introduced by standard alkylation or reductive amination techniques, such as those described above.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where

protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may

be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

In order to use a compound of the formula (I) or a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The pharmaceutical compositions of compounds of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions. A preferred route of administration is intravenously in sterile isotonic solution.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.05 to 75 mg/kg body weight (and preferably of 0.1 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I) as defined hereinbefore or a

pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in association with a pharmaceutically-acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a compound of the formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is a compound of formula (I) and pharmaceutically-acceptable salts or an *in vivo*-hydrolysable ester, amide or carbamate thereof, for use as a medicament to inhibit the [^{3}H]-emopamil binding site in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in the manufacture of a medicament for use in the inhibition of the [^{3}H]-emopamil binding site in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method of inhibiting of the [^{3}H]-emopamil binding site in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore.

The following Biological Test Methods, Data and Examples serve to illustrate the present invention.

Biological Test Methods

^{3}H-Emopamil binding to guinea pig liver membranes

The method of (-)-^{3}H-emopamil binding was a modification of Zech, C., Staudinger R., Mühlbacher, J. and Glossmann, H. Novel sites for phenylalkylamines: characterisation of a sodium-sensitive drug receptor with (-)-^{3}H-emopamil. Eur. J. Pharm. **208**: 119-130, 1991. The reaction mixture contained:

Assay buffer: 10 mM Tris-HCl, 0.1 mM phenylmethylsulphonyl fluoride (PMSF), 0.2% bovine serum albumin (BSA), pH 7.4 at 4 °C.

Radioligand: 0.96 nM (-)-^{3}H-emopamil (Amersham).

Guinea pig liver membranes: 40mg/mL original wet weight.

Compounds: 1-300 nM.

Total volume: 500 μL.

This mixture was incubated for 60 minutes at 37 °C. The incubation was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenimine (PEI) and washed three times with 5 mL of wash buffer containing 10 mM Tris-HCl, 10 mM $MgCl_2$, 0.2% BSA, pH 7.4 at 25 °C. Specific binding was defined with 10 μM emopamil. In general compounds with an IC_{50} below 300nM in this test were of interest.

Guinea-pig liver membrane preparation:

Male guinea pigs were sacrificed by CO_2 asphyxiation with dry ice. The livers were quickly excised and weighed and rinsed in membrane preparation buffer containing 10 mM Hepes, 1 mM Tris base-EDTA, 250 mM sucrose, pH 7.4. The livers were then minced, homogenised in 10 times volume with a motor driven Teflon-glass homogeniser with three strokes on ice. The homogenate was centrifuged at 1000 x g in a SS34 rotor for 5 minutes at 4 °C. The supernatant was filtered through 4 layers of gauze and then centrifuged at 8000 x g for 10 minutes at 4°C. This resulting supernatant was centrifuged at 40,000 x g for 15 minutes at 4 °C. The resulting pellet was resuspended in assay buffer and centrifuged again at 40,000 x g for 15 minutes at 4 °C. This pellet was resuspended in assay buffer (2.5 fold with respect to original wet weight) and homogenised with one stroke with the Teflon-glass homogeniser. Aliquots of 1 mL were stored at -70 °C.

^{3}H-D-888 binding to rat brain cortical membranes

The method of ^{3}H-D-888 binding was a modification of Reynolds, I.J., Snowman, A.M. and Synder, S.H. (-)-[^{3}H] Desmethoxyverapamil labels multiple calcium channel modular receptors in brain and skeletal muscle membranes: differentiation by temperature and dihydropyridines. J. Pharmacol. Exp. Ther. **237**: no.3, 731-738, 1986.

The assay tubes contained the following:

assay buffer: 50 mM Hepes, 0.2% BSA, pH 7.4

radioligand: 1ηM ^{3}H-D888 (Amersham)

rat cortical membranes: 6 mg/mL original wet weight

compounds: 0.3-100 μM

Total volume: 1000 μL.

This mixture was incubated for 60 minutes at 25 °C. The assay was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenamine (PEI) and washed three times with 5 mL of wash buffer containing 20 mM Hepes, 20 mM $MgCl_2$, pH 7.4. Specific binding was measured with 10 μM methoxyverapamil (D-600). This assay was used to determine in vitro selectivity of compounds vs. L-type voltage sensitive calcium channels, i.e. high affinity for the ^{3}H-D888 binding site would show a lack of selectivity.

Rat brain cortical membrane preparation

Male Sprague-Dawley Rats were sacrificed by decapitation and the brains were quickly excised. The cerebellum and brain stem were removed and discarded; and the rest of the brain was rinsed in 320 mM sucrose. The brain was then homogenised in a 10-fold volume of 320 mM sucrose with a motor driven Teflon-glass homogeniser using 10 strokes on ice. The homogenate was spun at 1000 x g for 10 minutes at 4 °C in a SS-34 rotor. The supernatant was then spun at 29,000 x g for 20 minutes. The resulting pellet was resuspended in membrane buffer (5 mM Hepes, 0.2% BSA, pH 7.4) to a final concentration of 60 mg original wet weight/mL.

Gerbil Global Model of Cerebral Ischaemia

Male Mongolian gerbils (Charles River) weighing 60-70 grams are used in these experiments. They are housed in individual cages with food (Purina Rodent Chow) and water available *ad libitum*. The animal room is maintained at 23 ± 2 °C, and is on an automatic 12 hour light cycle.

The gerbils are brought to the surgical suite and dosed intraperitoneally with the test agent or vehicle, forty five minutes prior to surgery. Drugs are administered at a volume of 5 mL/kg (intraperitoneal). Vehicle is generally saline, with sodium phosphate added to adjust pH, if needed. Forty-five minutes after dosing the gerbils are anaesthetised with halothane (3.3%) which is delivered along with oxygen (1.5 l/M) through a face mask. After the gerbils are anaesthetised, halothane is continued at a maintenance level of 1.5-2 % along with oxygen. The ventral surface of the neck is shaved and cleaned with alcohol. Surgical procedures are carried out on a thermostat-controlled heating pad set to 37 °C. An incision is made in the neck, the carotid arteries are dissected away from the surrounding tissue, and isolated with a 5 cm length of Silastic tubing. When both arteries have been isolated they are

clamped with microaneurysm clips (Roboz Instruments). The arteries are visually inspected to determine that the blood flow has been stopped. After 5 minutes the clips are gently removed from the arteries and blood flow begins again. A sham control group is treated identically but is not subjected to carotid artery occlusion. The incisions are closed with suture and the gerbils removed from the anaesthesia masks and placed on another heating pad to recover from the anaesthesia. When they have regained the righting reflex and are beginning to walk around, they are again dosed with the test compound and returned to their home cages. This occurs approximately five minutes after the end of surgery.

Twenty-four hours post ischaemia gerbils are tested for spontaneous locomotor activity, using a Photobeam Activity System from San Diego Instruments. They are individually placed in Plexiglas chambers measuring 27.5 cm x 27.5 cm x 15 cm deep. The chambers are surrounded by photocells, and every time a beam is broken one count is recorded. Each gerbil is tested for two hours, and cumulative counts are recorded at 30, 60, 90, and 120 minutes. Mean counts are recorded for each group and drug groups are compared to control with an ANOVA and Bonferroni post test. After each gerbil is tested it is returned to its home cage. At this time gerbils are also observed for any changes from normal behaviour.

For the next two days no specific testing is performed, but the gerbils are observed two to three times per day for any unusual behaviours or obvious neurological symptoms (i.e. ataxia, convulsions, stereotypic behaviour). Four days post ischaemia the gerbils are sacrificed by decapitation and their brains removed and preserved in 10% buffered formalin. Brains were removed, fixed and stained with hematoxylin and eosin. Under a light microscope, hippocampal fields were observed and graded for damage to the CA1 subfield: 0 to 4 scale, with 0 representing no damage and 4 representing extensive damage.

Transient focal ischaemia in rats

The method was as described by Lin, T-N., He, Y.Y., Wu, G., Khan, M. And Hsu, C.Y. Effect of brain edema on infarct volume in a focal model cerebral ischaemia model in rats. Stroke **24**:117-121, 1993, which model is considered to be relevant to the clinical situation. Male Long-Evans rats 250-350 g were used. Surgery leading to focal ischaemia was conducted under anaesthesia with 100 mg/kg ketamine and 5 mg/kg i.m. xylazine. Rectal temperature was monitored and maintained at 37.0 $\pm$ 0.5 °C. The right middle cerebral artery (MCA) was exposed using microsurgical techniques. The MCA trunk was ligated

immediately above the rhinal fissure with 10-0 suture. Complete interruption of blood flow was confirmed under an operating microscope. Both common carotid arteries were then occluded using nontraumatic aneurysm clips. After a predetermined duration of ischaemia (45 min), blood flow was restored in all three arteries. Twenty-four hours post occlusion, rats were killed under ketamine anaesthesia by intracardiac perfusion with 200 mL of 0.9% NaCl. The brain was removed and processed with 2% triphenyltetrazolium chloride to identify and quantitate the infarcted brain region. Compounds were administered by intravenous infusion for 4 hours.

Data

The following results were obtained in the ^{3}H-Emopamil binding to guinea pig liver membranes test.

Example	**IC_{50} (nM)**
3	24
14	105.5
13	243

Examples

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated:-

(i) concentrations were carried out by rotary evaporation *in vacuo*;

(ii) operations were carried out at ambient temperature, that is in the range 18-26 °C and under a nitrogen atmosphere otherwise stated;

(iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the formula I were generally confirmed by NMR and mass spectral techniques - proton magnetic resonance spectra were determined in DMSO-δ_6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz; chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; bs, broad singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, dt, double of

triplets, m, multiplet; bm, broad multiplet and unless otherwise stated ^{1}H NMR is quoted; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected, in this application, $(M+H)^+$ is quoted unless otherwise stated;

(vi) intermediates were not generally fully characterized and purity was in general assessed mass spectral (MS) or NMR analysis; and

(vii) in which the following abbreviations (also used hereinabove) may be used :-

DMSO	is dimethylsulphoxide;
$CDCl_3$	is deuterated chloroform;
m/s	is mass spectroscopy;
THF	is tetrahydrofuran;
DCM	is dichloromethane;
Com Av	is commercially available; and
SM	is starting material.

Example 1

4-[2-(Piperidin-1-yl)ethyl(*N*-methyl)amino]thiochroman

To a solution of 4-[2-(piperidin-1-yl)ethylamino]thiochroman (Reference Example 1) (1.27 g, 4.59 mmol) in 46 mL of THF was added triethylamine (1.34 mL, 9.64 mmol), followed by ethyl chloroformate (485 μL, 5.05 mmol). A white precipitate was formed immediately. The reaction was stirred at room temperature for 1h. Solvents were then removed *in vacuo*. The residue was taken up in water (50 mL) and ether (50 mL). The aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (1 x 50 mL), water (1 x 50 mL) and brine (1 x 50 mL) and dried over $MgSO_4$. Removal of solvents yielded a light yellow liquid. The yellow liquid was dissolved in 32 mL of THF and lithium aluminium hydride (749 mg, 19.7 mmol) was added in small portions. After addition was complete, the reaction was heated to reflux. After 2h, the reaction was cooled and quenched with $Na_2SO_4.10H_2O$. The mixture was stirred until all the solids had turned white. It was then filtered through a small pad of Celite. Solvents were removed to afford a yellow liquid. Purification by silica gel chromatography (20:1 DCM/2M ammonia in methanol) yielded the title compound as a yellow liquid (1.15 g,

86%). NMR ($CDCl_3$): 1.43 (m, 2H), 1.57 (m, 4H), 2.27-2.06 (m, 2H), 2.28 (s, 3H), 2.71-2.33 (m, 8H), 3.08 (m, 2H), 3.77 (dd, 1H), 7.05 (m, 3H), 7.59 (d, 1H); m/s: 291.

Example 2

4-[2-(morpholino)ethyl(*N*-methyl)amino]thiochroman

Formaldehyde (37 wt% in H_2O, 3.5 mL, 46.8 mmol) was added to a solution of 4-[2-(morpholino)ethylamino]thiochroman (Reference Example 2) (500 mg, 1.80 mmol) in methanol (11 mL) and the reaction was stirred for 1h at room temperature. The reaction was then cooled in an ice bath and sodium borohydride (611 mg, 16.2 mmol) was added slowly. When addition was complete, the ice bath was removed and the reaction was allowed to stir at room temperature overnight. Solvents were then removed *in vacuo*. The residue was taken up in water (30 mL) and DCM (30 mL). The aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine (1 x 50 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* to yield a yellow liquid. Purification by silica gel chromatography (25:1 DCM/2M ammonia in methanol) afforded the title compound as a yellow liquid (379 mg, 72%). NMR ($CDCl_3$): 2.09 (m, 1H), 2.22 (m, 1H), 2.30 (s, 3H), 2.60-2.42 (m, 7H), 2.65 (m, 1H), 3.08 (m, 2H), 3.70 (m, 4H), 3.77 (dd, 1H), 7.05 (m, 3H), 7.58 (m,1H); m/s: 293.

Example 3

4-[2-(Piperidin-1-yl)ethyl(*N*-ethyl)amino]thiochroman

A solution of 4-[2-(piperidin-1-yl)ethyl(*N*-acetyl)amino]thiochroman (Method 1) (360 mg, 1.13 mmol) in 15 mL of THF was cooled to 0 °C and borane-methyl sulfide complex (2.0M in toluene, 1.4 mL, 2.8 mmol) was added. The reaction mixture was then heated to reflux. After 3h, the reaction was cooled and 3 mL of methanol was added. 1M aqueous HCl (15 mL) was added and the reaction was heated to reflux for 1h. The reaction was then cooled and the pH was adjusted to 14 with 1M NaOH solution. The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$. Solvents were removed to yield a yellow liquid. Purification by silica gel chromatography (20:1 DCM:2M ammonia in methanol) afforded a yellow liquid (263 mg, 76%). NMR ($CDCl_3$): 1.04 (t, 3H), 1.42 (m, 2H), 1.55 (m, 4H), 2.00 (m, 1H), 2.60-2.28 (m, 10H), 2.70 (m, 1H), 3.07 (m, 2H), 3.90 (dd, 1H), 7.06 (m, 3H), 7.70 (m, 1H); m/s: 305.

Example 4

4-[2-(morpholino)ethyl(*N*-allyl)amino]thiochroman

To a solution of 4-[2-(morpholino)ethylamino]thiochroman (Reference Example 2) (500 mg, 1.80 mmol) in 3.6 mL of THF was added allyl bromide (311 μl, 3.59 mmol), followed by triethylamine (501 μl, 3.59 mmol) and the reaction was heated to reflux for 17h. A yellow precipitate had formed and the reaction was cooled. Purification by silica gel chromatography (20:1 DCM:2M ammonia in methanol) afforded the title compound as a yellow liquid (143 mg, 25%). NMR ($CDCl_3$): 1.96 (m, 1H), 2.60-2.25 (m, 8H), 2.70 (m, 1H), 3.05 (m, 3H), 3.25 (m, 1H), 3.68 (t, 4H), 3.95 (dd, 1H), 5.09 (d, 1H), 5.21 (dd, 1H), 5.82 (m, 1H), 7.06 (m, 3H), 7.71 (m, 1H); m/s: 319.

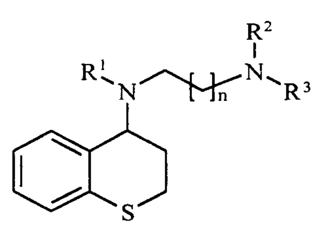
Example 5

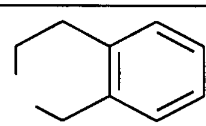
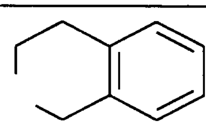
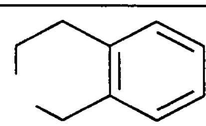
(-)-4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethylamino]thiochroman

To a suspension of (-)-4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)acetamido] thiochroman (Method 3) (868 mg, 2.56 mmol) in 17 mL of THF was added lithium aluminium hydride (389 mg, 10.3 mmol) and the reaction was heated to reflux. After 23h, the reaction was cooled and $Na_2SO_4.10H_2O$ was added to quench the reaction. The suspension was then stirred overnight until all the salts had turned white. The mixture was then filtered through $MgSO_4$ and solvents were removed to yield a yellow liquid. Purification by silica gel chromatography (20:1 DCM:2M ammonia in methanol) yielded the title compound as a yellow liquid (756 mg, 90%). NMR ($CDCl_3$): 1.95 (m, 1H), 2.33 (m, 1H), 2.67 (m, 4H), 2.86 (m, 5H), 3.34 (td, 1H), 3.60 (s, 2H), 3.79 (m, 1H), 7.01 (m, 2H), 7.11 (m, 6H); m/s: 325; $[a]_D$ = -83° (c = 0.0066, MeOH).

Examples 6-19

Using an analogous procedure to that described in Examples 1-5 and Reference Example 1 (see below), the following compounds were prepared.



Ex	R[1]	R[2]	R[3]	n	Made by Ex	m/s	SM
6	H	$-(CH_2)_2O(CH_2)_2-$		2	Ref. 1	293	
7	H	Me	Me	1	Ref. 1	237	
8	H	$(CH_3)_2CH-$	H	1	Ref. 1	251	
9	H	$-(CH_2)_4-$		1	Ref. 1	263	
10	H	Et	Et	1	Ref. 1	265	
11	H	$-(CH_2)_5-$		2	Ref. 1	291	
12	H	$-(CH_2)_2N(Me)(CH_2)_2-$		2	Ref. 1	306	
13[1]	H	Ph	H	1	Ref. 1		
14	H	$PhCH_2$	H	1	Ref. 1	299	
15	Me	$-(CH_2)_2N(Me)(CH_2)_2-$		2	Ex. 2	320	Ex 12
16	Et	$-(CH_2)_2O(CH_2)_2-$		1	Ex. 3	307	M 2 *
17[2]	H			1	Ex. 5	325	M 4
18[3]	Me			1	Ex. 1	339	Ex 5
19[4]	Me			1	Ex. 1	339	Ex 19

* Free base used as starting material.

[1] Calc'd for $C_{17}H_{20}N_2S$:C, 71.79; H, 7.09; N, 9.85, Found: C, 71.52; H, 7.06; N, 9.52.

[2] (+)-enantiomer; $[a]_D = +100°$ (c=0.0062, MeOH).

[3] (+)-enantiomer;$[a]_D = +10°$ (c=0.01, MeOH).

[4] (-)-enantiomer;$[a]_D = -9°$ (c=0.01, MeOH).

NMR ($CDCl_3$) results:

Example 6: 4-(3-Morpholin-4-ylpropylamino)thiochroman, 1.68 (m, 2H), 1.93 (m, 1H), 2.40 (m, 7H), 2.70 (m, 2H), 2.87 (dt, 1H), 3.34 (td, 1H), 3.68 (t, 4H), 3.74 (m, 1H), 7.20-6.99 (m, 4H).

<u>Example 7:</u> 4-(2-Dimethylaminoethylamino)thiochroman, 2.00-1.94 (m, 2H), 2.21 (s, 6H), 2.48-2.31 (m, 3H), 2.87-2.71 (m, 3H), 3.37 (m, 1H), 3.76 (m, 1H), 7.18-6.99 (m, 4H).

<u>Example 8:</u> 4-(2-Isopropylaminoethylamino)thiochroman, 1.06 (d, 6H), 1.76 (br s, 2H), 1.93 (m, 1H), 2.32 (m, 1H), 2.89-2.66 (m, 6H), 3.35 (td, 1H), 3.77 (m, 1H), 7.19-6.96 (m, 4H).

<u>Example 9:</u> 4-((2-Pyrrolidin-1-ylethyl)amino)thiochroman, 1.60 (br s, 1H), 1.75 (m, 4H), 1.94 (m, 1H), 2.33 (m, 1H), 2.46 (m, 4H), 2.87-2.55 (m, 5H), 3.36 (td, 1H), 3.77 (t, 1H), 7.13-6.97 (m, 3H), 7.16 (d, 1H).

<u>Example 10:</u> 4-(2-Diethylaminoethylamino)thiochroman, 0.98 (t, 6H), 1.95 (m, 1H), 2.31 (m, 1H), 2.52 (q, 4H), 2.55 (t, 2H), 2.71 (m, 2H), 2.86 (dt, 1H), 3.36 (td, 1H), 3.75 (dd, 1H), 7.18-6.97 (m, 4H).

<u>Example 11:</u> 4-((3-Piperidin-1-ylpropyl)amino)thiochroman, 1.80-1.30 (m, 9H), 1.92 (m, 1H), 2.32 (m, 6H), 2.68 (m, 2H), 2.85 (m, 1H), 3.35 (td, 1H), 3.74 (m, 1H), 7.20-6.98 (m, 4H).

<u>Example 12:</u> 4-((3-(4-Methylpiperazin-1-yl)propyl)amino)thiochroman, 1.69 (m, 2H), 1.92 (m, 1H), 2.27 (s, 3H), 2.42 (m, 11H), 2.72 (m, 2H), 2.86 (dt, 1H), 3.34 (td, 1H), 3.73 (t, 1H), 7.18-6.97 (m, 4H).

<u>Example 13:</u> 4-(2-Phenylaminoethylamino)thiochroman, 1.55 (br s, 1H), 1.97 (m, 1H), 2.31 (m, 1H), 2.97-2.84 (m, 3H), 3.23 (m, 2H), 3.33 (m, 1H), 3.79 (m, 1H), 4.14 (br s, 1H), 6.74-6.59 (m, 3H), 7.21-7.00 (m, 6H).

<u>Example 14:</u> 4-(2-Benzylaminoethylamino)thiochroman, 1.52 (br s, 2H), 1.94 (m, 1H), 2.30 (m, 1H), 2.88-2.73 (m, 5H), 3.34 (td, 1H), 3.74 (t, 1H), 3.77 (s, 2H), 7.35-6.98 (m, 9H).

<u>Example 15:</u> 4-(Methyl-(3-(4-methylpiperazin-1-yl)propyl)amino)thiochroman, 1.68 (m, 2H), 2.12 (m, 2H), 2.22 (s, 3H), 2.29 (s, 3H), 2.58-2.34 (m, 12H), 3.07 (m, 2H), 3.75 (dd, 1H), 7.08-6.99 (m, 3H), 7.55 (m, 1H).

<u>Example 16:</u> 4-(Ethyl-(2-morpholin-4-yl-ethyl)amino)thiochroman, 1.05 (t, 3H), 2.02 (m, 1H), 2.28 (m, 1H), 2.68-2.41 (m, 10H), 3.06 (m, 2H), 3.68 (t, 4H), 3.91 (dd, 1H), 7.06 (m, 3H), 7.70 (m, 1H).

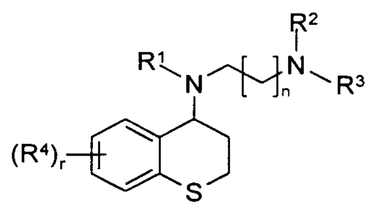
<u>Example 17:</u> (*R*)-4-(2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)ethyl)amino)thiochroman, 1.95 (m, 1H), 2.33 (m, 1H), 2.69 (m, 4H), 2.85 (m, 5H), 3.34 (td, 1H), 3.60 (s, 2H), 3.79 (m, 1H), 6.99 (m, 2H), 7.11 (m, 6H).

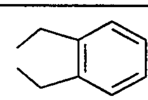
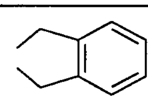
Example 18: (*S*)-4-(*N'*-(2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-*N'*-ethyl)amino)thiochroman, 2.12 (m, 1H), 2.24 (m, 1H), 2.32 (s, 3H), 2.73 (m, 6H), 2.89 (t, 2H), 3.10 (dd, 2H), 3.62 (s, 2H), 3.81 (dd, 1H), 7.15-6.97 (m, 7H), 7.62 (m, 1H).

Example 19: (*R*)-4-(*N'*-(2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-*N'*-ethyl)amino)thiochroman, 2.12 (m, 1H), 2.26 (m, 1H), 2.33 (s, 3H), 2.81-2.64 (m, 6H), 2.89 (t, 2H), 3.08 (t, 2H), 3.62 (s, 2H), 3.81 (dd, 1H), 7.12-6.97 (m, 7H), 7.60 (d, 1H).

Examples 20-25

Using an procedure analogous to that described in Example 5 compounds of Examples 20, 21, 23, 24 and 25 were prepared. Example 22 was prepared by the method of Example 1.



Ex	R^1	R^2	R^3	n	m/s	SM
20[1]	Me	Me	$-CH_2Ph$	1	327	Ex. 29
21[1]	Me	$-CH_2(CH_2)_2CH_2-$		1	277	Ex. 30
22[1]	Me			1	325	Ex. 22
23[1]	H			1	311	M. 6
24[1]	H	$-CH_2(CH_2)_4CH_2-$		1	291	Ex. 32
25[1]	H	Me	$-CH_2Ph$	1	313	Ex. 33

[1] S Enantiomer

SM - starting material

NMR (DMSO) results:

Example 20: (*S*)-4-(*N*-2-(*N'*-Benzyl-*N'*-methylamino)ethyl(*N*-methyl)amino)thiochroman, 1.84-2.00 (m, 1H), 2.06-2.20 (m, 7H), 2.40-2.60 (m, 4H), 3.01-3.11 (m, 2H), 3.46 (s, 2H), 3.70-3.79 (m, 1H), 6.96-7.13 (m, 3H), 7.19-7.35 (m, 5H), 7.54 (d, 1H).

Example 21: (*S*)-4-(*N'*-Methyl-*N'*-(2-pyrrolidin-1-ylethyl)amino)thiochroman, 1.59-1.69 (m, 4H), 1.86-2.01 (m, 1H), 2.05-2.23 (m, 4H), 2.35-2.60 (m, 8H), 3.02-3.13 (m, 2H), 3.70-3.80 (m, 1H), 6.97-7.12 (m, 3H), 7.53-7.61 (m, 1H).

Example 22: (*S*)-4-(*N'*-(2-(1,3-Dihydroisoindol-2-yl)ethyl)-*N'*-methylamino)thiochroman, 1.88-2.05 (m, 1H), 2.10-2.29 (m, 4H), 2.53-2.67 (m, 2H), 2.71-2.90 (m, 2H), 3.03-3.13 (m, 2H), 3.75-3.90 (m, 5H), 6.96-7.26 (m, 7H), 7.58 (d, 1H).

Example 23: (*S*)-4-(*N'*-(2-(1,3-Dihydroisoindol-2-yl)ethyl)amino)thiochroman, 1.72-1.93 (m, 2H), 2.20-2.31 (m, 1H), 2.63-2.91 (m, 5H), 3.22-3.38 (m, 1H), 3.72-3.79 (m, 1H), 3.84 (s, 4H), 6.95-7.32 (m, 8H).

Example 24: (*S*)-4-((2-Azepan-1-ylethyl)amino)thiochroman, 1.37-1.67 (m, 8H), 1.67-1.92 (m, 2H), 2.15-2.31 (m, 1H), 2.31-2.73 (m, 8H), 2.77-2.90 (m, 1H), 3.20-3.48 (m, 1H), 3.69 (m, 1H), 6.93-7.30 (m, 4H).

Example 25: (*S*)-4-(2-(*N'*-Benzyl-*N'*-methylamino)ethylamino)thiochroman, 1.70-1.85 (m, 2H), 2.09 (s, 3H), 2.16-2.30 (m, 1H), 2.40-2.55 (m, 2H), 2.58-2.89 (m, 3H), 3.20-3.53 (m, 3H), 3.65-3.73 (m, 1H), 6.96-7.36 (m, 9H).

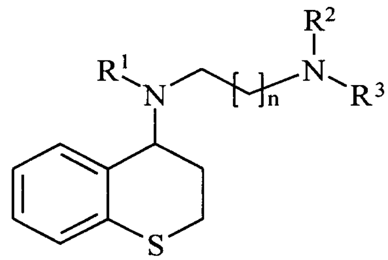
Example 26

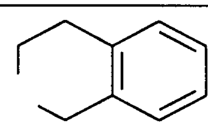
4-[2-(Piperidin-1-yl)ethyl(*N*-methyl)amino]thiochroman bismaleate salt

A solution of 4-[2-(piperidin-1-yl)ethyl(*N*-methyl)amino]thiochroman (Example 1) (1.15 g, 3.96 mmol) in 10 mL of ether was added to a solution of maleic acid (965 mg, 8.31 mmol) in 80 mL of ether. The mixture was stirred for 30 min and then allowed to stand. After several days, a white solid had formed. This was triturated with ether and then filtered and dried to yield the bismaleate (1.77 g, 85%). NMR: 1.51 (m, 2H), 1.70 (m, 4H), 2.09 (m, 2H), 2.20 (s, 3H), 2.70 (m, 1H), 2.85 (m, 1H), 3.29-3.08 (m, 8H), 3.83 (t, 1H), 6.15 (s, 4H), 7.09 (m, 3H), 7.52 (d, 1H). m/s: 291.

Examples 27 and 28

Using the procedure of Example 26, salts of the Examples were prepared. The following bismaleate salts are provided by way of illustration:



Ex	R^1	R^2	R^3	n	m/s	SM
27	H	$-(CH_2)_2O(CH_2)_2-$		1	279	Ref Ex 2
28[1]	Me			1	339	Ex 20

[1] (-) enantiomer; $[a]_D$ = -17° (c=0.01, MeOH)

NMR results:

Example 27: 2.07 (m, 1H), 2.58 (m, 5H), 2.69 (m, 2H), 3.35-3.00 (m, 4H), 3.64 (m, 4H), 4.48 (m, 1H), 6.13 (s, 4H), 7.32-7.14 (m, 3H), 7.44 (m, 1H).

Example 28: 2.09 (m, 2H), 2.24 (s, 3H), 2.78 (m, 1H), 3.17-2.93 (m, 6H), 3.29 (m, 1H), 3.41 (m, 2H), 3.89 (t, 1H), 4.36 (s, 2H), 6.14 (s, 4H), 7.11 (m, 4H), 7.25 (m, 3H), 7.54 (d, 1H).

REFERENCE EXAMPLES

Reference Example 1

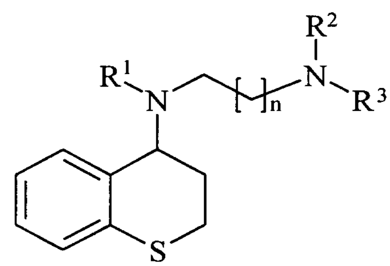
4-[2-(Piperidin-1-yl)ethylamino]thiochroman

To a solution of thiochroman-4-one (4.15 g, 25.3 mmol) in toluene (70 mL) at 0 °C was added 1-(2-aminoethyl)piperidine (20 g, 156 mmol), followed by dropwise addition of titanium(IV) tetrachloride (1.0 M in toluene, 12 mL, 12 mmol). The addition of titanium(IV) tetrachloride was kept at a rate such that the temperature of the reaction mixture was kept below 10 °C. When addition was complete, the reaction was allowed to warm to room temperature. After 5h, the reaction mixture was filtered through Celite, rinsing the residue with toluene. Solvents were then removed *in vacuo* to yield a yellow liquid. The yellow liquid was then taken up in methanol (50 mL) and sodium borohydride (960 mg, 25.3 mmol) was added in small portions over 5 min. The reaction was then stirred at room temperature for 45 min. It was then added to water (75 mL) and ether (75 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were then washed with brine (1 x 100 mL) and dried over $MgSO_4$. Solvents were removed *in vacuo* to

yield a yellow liquid. Purification with silica gel chromatography (20:1 DCM:methanol, 1% NH_4OH) yielded the title compound as a yellow liquid (4.27 g, 61%). NMR ($CDCl_3$): 1.44 (m, 2H), 1.56 (m, 4H), 2.29-1.86 (m, 2H), 2.35 (m, 4H), 2.46 (m, 2H), 2.75 (m, 2H), 2.86 (dt, 1H), 3.36 (td, 1H), 3.76 (t, 1H), 7.19-6.99 (m, 4H); m/s: 277.

Reference Example 2

Using an analogous procedure to that described in Reference Example 1, the following compound was prepared.



Ref Ex	**R^1**	**R^2**	**R^3**	**n**	**m/s**
2	H	$-(CH_2)_2O(CH_2)_2-$		1	279

NMR ($CDCl_3$) Results: 1.96 (m, 1H), 2.62-2.24 (m, 7H), 2.76 (m, 2H), 2.90 (m, 1H), 3.35 (td, 1H), 3.66 (m, 4H), 3.78 (m, 1H), 7.16-7.00 (m, 4H)

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of the starting materials used in the above reactions.

Method 1

4-[2-(Piperidin-1-yl)ethyl(*N*-acetyl)amino]thiochroman

To a solution of 4-[2-(piperidin-1-yl)ethylamino]thiochroman (Reference Example 1) (500 mg, 1.81 mmol) in 18 mL of DCM was added triethylamine (279 μL, 2.00 mmol), followed by acetyl chloride (142 μL, 2.00 mmol). The reaction was then stirred at room temperature. After 5h, the reaction was added to water (20 mL) and extracted with ether (2 x 20 mL). The combined organic layers were dried over Na_2SO_4. Solvents were removed to yield a colorless liquid. Purification by silica gel chromatography (20:1 DCM:2 M ammonia

in methanol) afforded the title compound (490 mg, 85%). NMR: 1.35 (m, 6H), 2.05 (s, 1.5H), 2.13 (s, 1.5H), 2.14 (m, 8H), 3.36-2.70 (m, 4H), 5.05 (dd, 0.5H), 5.29 (m, 0.5H), 7.15-7.00 (m, 4H); m/s: 319.

Method 2

4-[2-(Morpholino)ethyl(*N*-acetyl)amino]thiochroman

To a solution of 4-[2-(morpholino)ethylamino]thiochroman (Reference Example 2) (500 mg, 1.80 mmol) in 18 mL of DCM added acetyl chloride (141 µl, 1.98 mmol) followed by triethylamine (276 µl, 1.98 mmol) and the reaction was stirred overnight. The reaction was then added to saturated NH_4Cl solution (30 mL) and ether (30 mL). The aqueous layer was extracted with ether (2 x 30 mL) and the combined organic layers were washed with water (1 x 30 mL) and brine (1 x 30 mL) and dried over $MgSO_4$. Solvents were removed to yield a yellow liquid. Purification by silica gel chromatography (20:1 DCM:2 M ammonia in methanol) afforded the free base of the title compound as a yellow liquid (505 mg, 87%). The yellow liquid (200 mg, 0.624 mmol) was taken up in 5 mL of ether and maleic acid (87 mg, 0.749 mmol) in 8 mL of ether was added. A white precipitate was formed initially which settled down to a yellow oil. After 3 days of standing, the yellow oil had solidified to a light yellow solid - 4-[2-(morpholino)ethyl(*N*-acetyl)amino]thiochroman maleate salt - which was collected by filtration and dried under vacuum. NMR: 2.51-2.16 (m, 5H), 3.90-2.63 (m, 14H), 5.15 (m, 1H), 6.10 (s, 2H), 7.20-6.94 (m, 4H); m/s: 321.

Method 3

(-)-4-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)acetamido]thiochroman

To a solution of (-)-4-[2-chloroacetamido]thiochroman (Method 5) (750 mg, 3.10 mmol) in 18 mL of acetonitrile was added 1,2,3,4-tetrahydroisoquinoline (1.2 mL, 9.3 mmol) and the reaction was heated to reflux for 4h. The reaction mixture was cooled and then added to DCM/ether (75 mL) and saturated $NaHCO_3$ solution (25 mL). The organic layers were washed with brine (1 x 40 mL) and dried over Na_2SO_4. Removal of solvents gave a yellow solid which was triturated with ether. The light yellow solid was collected by filtration and dried under vacuum (904 mg, 86%). NMR ($CDCl_3$): 2.20 (m, 1H), 2.35 (m, 1H), 2.81 (m, 4H), 3.00 (m, 2H), 3.23 (s, 2H), 3.71 (s, 2H), 5.24 (m, 1H), 7.24-6.97 (m, 7H), 7.50 (m, 1H); m/s: 339; $[a]_D$ = -92° (c = 0.0088, MeOH).

Method 4

(-)-4-[2-chloroacetamido]thiochroman

To a solution of (-)-4-aminothiochroman (Method 5) (1.00 g, 6.05 mmol) and 2,6-lutidine (1.27 mL, 10.9 mmol) in 23 mL of DCM at 0 °C was added chloroacetyl chloride (770 µL, 9.68 mmol) dropwise. After 5h, the resulting yellow solution was added to water (20 mL) and DCM (20 mL). The aqueous layer was extracted again with DCM (1 x 20 mL). The combined organic layers were washed with 1M HCl solution (1 x 50 mL), water (1 x 50 mL) and brine (1 x 50 mL) and dried over Na_2SO_4. Solvents were removed to yield a yellow solid which was triturated with ether to give the title compound as a white solid (850 mg, 58%). NMR ($CDCl_3$): 2.18 (m, 1H), 2.40 (m, 1H), 3.03 (m, 2H), 4.10 (s, 2H), 5.22 (m, 1H), 6.77 (m, 1H), 7.23-7.04 (m, 3H); $[a]_D$ = -150° (c = 0.0094, MeOH).

Method 5

(+)-4-[2-chloroacetamido]thiochroman and (-)-4-aminothiochroman

To dimethoxyethane (700 mL) was added 4-aminothiochroman (78 gram, 0.473 mole), isopropylchloroacetate (40 gram, 0.293 mole) and CHIRAZYME L-2 lipase attached to carrier-2 (16 grams, obtained from Roche Diagnostics GmbH, Germany). The head space was flushed with nitrogen and the mixture gently stirred at room temperature for 5.5 hours. The enzyme was removed by filtering the reaction mixture through a Whatman 113 filter paper, the enzyme was then rinsed with dimethoxyethane (400 mL) and the filtrates combined and concentrated to 600 mL by evaporation under reduced pressure at a water bath temperature of 30 °C. To the concentrated dimethoxyethane solution was added 1 molar HCl (1200 mL) over a period of 15 minutes resulting in the precipitation of the reaction product (+)-4-[2-chloroacetamido]thiochroman. The solid was resuspended in 1 molar HCl (2000 mL), recovered by filtration, washed in water (2000 mL), recovered by filtration and dried under vacuum at room temperature. The yield of (+)-4-[2-chloroacetamido]thiochroman was 51 grams (0.21 moles, 90% yield of enantiomer). The filtrate from the HCl precipitation step was stored at 4 °C for 16 hours during which time further precipitate of (+)-4-[2-chloroacetamido]thiochroman occurred, this was removed by filtration through a Whatman 113 filter paper and the clear filtrate adjusted to pH 12 with sodium hydroxide (40% w/v). The solution was then extracted with n-hexane (2 x 1000 mL) to recover unreacted (-)-4-aminothiochroman.The hexane was recovered, dried with anhydrous sodium sulphate and

filtered. The hexane was then removed under vacuum initially at a water bath temperature of 30 °C and then finally by holding at 50 °C for 30 minutes yielding a cloudy, yellow/brown, semi-solid residue (25.7 grams). Kugelrohr distillation yielded a light yellow liquid, (-)-4-aminothiochroman, (bp 85-95 °C, 50-60 mTorr). [a]= -110° (c=0.49, MeOH).

Enantiomeric purity of (+)-4-[2-chloroacetamido]thiochroman was determined directly by gas chromatography using the conditions outlined below. The amine was analysed under the same conditions after conversion to (-)-4-acetylaminothiochroman by treatment with acetic anhydride.

Column - Chrompak WCOT fused silica 25 m x 0.32 mm, coating CP Chirasil-Dex CB; Carrier - Helium; Temperature - 180 °C isothermal; Retention times - (-)-4-acetylaminothiochroman, 16 minutes and 17.2 minutes and (+)-4-[2-chloroacetamido]thiochroman, 25.9 minutes and 26.5 minutes.

Method 6

(a) A suspension of *N*-(*t*-butoxycarbonyl)glycine (2.35, 1.34 x 10^{-2} mole) and 1-hydroxybenzotriazole (1.90 g, 1.41 x 10^{-2} mole) in DCM (50 mL) was treated with 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.05 g, 1.59 x 10^{-2} mole) and triethylamine (2.3 mL, 1.65 x 10^{-2} mole), respectively. Immediately, a solution of (*S*)-4-aminothiochroman (2.18 g, 1.32 x 10^{-2} mole) in DCM (30 mL) was added. After stirring at ambient temperature for 23 hours, the reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to yellow oil which was purified by chromatography, eluting with 2:1 ethyl acetate:hexane (v:v), to give the product as a white foam (4.25 g, 99%). ^{1}H NMR (DMSO): 1.38 (s, 9H), 1.92-2.17 (m, 2H), 2.96-3.14 (m, 2H), 3.44-3.63 (m, 2H), 4.93-5.06 (m, 1H), 6.87-7.24 (m, 5H), 8.24 (d, 1H).

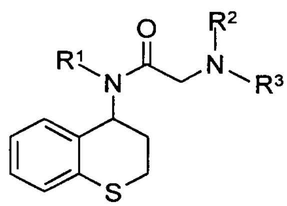
(b) A solution of the white foam from (a) (2.18 g, 6.76 x 10^{-3} mole) in THF (35 mL) was treated with concentrated hydrochloric acid (2 mL) and heated at 60 °C for two hours. The reaction mixture was partitioned between 1N aqueous sodium hydroxide solution and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to a white solid. The solid was dissolved in DCM and purified by chromatography, eluting with 10% 2.0 M ammonia in methanol:90% DCM (v/v), to give the product as a white solid (1.39 g, 93%). ^{1}H NMR (DMSO): 1.91-2.27

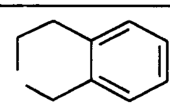
(m, 4H), 2.97-3.20 (m, 4H), 4.96-5.07 (m, 1H), 6.99-7.23 (m, 4H), 8.18 (d, 1H). m/s: 223.

(c) A suspension of the white solid from (b) (1.39 g, 6.25 x 10^{-3} mole) and sodium carbonate (1.98 g, 1.88 x 10^{-2} mole) in THF (32 mL) was treated with α,α'-dibromo-*o*-xylene (1.66 g, 6.29 x 10^{-3} mole) followed by refluxing for five hours. The reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to a white solid. The solid was dissolved in DCM/methanol and purified by chromatography, eluting with 5% 2.0 M ammonia in methanol:95% DCM (v/v), to give the product as a white solid (1.93 g, 95%). ^{1}H NMR (DMSO): 1.97-2.26 (m, 2H), 2.98-3.15 (m, 2H), 3.42 (s, 2H), 4.01 (s, 4H), 5.00-5.12 (m, 1H), 7.01-7.29 (m, 8H), 8.34 (d, 1H). m/s: 325.

Examples 29-33

Compounds of Examples 29-33 of the formula below were made by the procedure of Method 3, above.



Ex	R^1	R^3	R^3	m/s
29[1]	Me	Me	$-CH_2Ph$	341
30[1]	Me	$-CH_2(CH_2)_2CH_2-$		291
31[1]	H			325
32[1]	H	$-CH_2(CH_2)_4CH_2-$		305
33[1]	H	Me	$-CH_2Ph$	327

[1] S Enantiomer

NMR (DMSO) results:

Example 29: 2.03-2.27 (m, 5H), 2.50 (s, 1.2H), 2.75 (s, 1.8H), 2.94-3.06 (m, 1H), 3.10-3.70 (m, 5H), 5.23-5.33 (m, 0.4H), 5.61-5.72 (m, 0.6H), 6.88-7.43 (m, 9H).

Example 30: 1.59-1.77 (m, 4H), 2.05-2.34 (m, 2H), 2.43-2.61 (m, 5.2H), 2.75 (s, 1.8H), 2.95-3.07 (m, 1H), 3.20-3.46 (m, 3H), 5.33-5.42 (m, 0.4H), 5.59-5.70 (m, 0.6H), 6.88-7.18 (m, 4H).

Example 31: NMR ($CDCl_3$): 2.19 (m, 1H), 2.34 (m, 1H), 2.81 (m, 4H), 2.98 (m, 2H), 3.23 (s, 2H), 3.66 (s, 2H), 5.24 (m, 1H), 7.22-6.97 (m, 7H), 7.50 (m, 1H); m/s: 339; $[a]_D = +91°$ (c = 0.0058, MeOH).

Example 32: 1.43-1.65 (s, 8H), 1.95-2.24 (m, 2H), 2.57-2.73 (m, 4H), 3.00-3.17 (m, 4H), 4.95-5.10 (m, 1H), 7.00-7.22 (m, 4H), 7.96-8.09 (m, 1H).

Example 33: 1.96-2.25 (m, 5H), 2.96-3.10 (m, 4H), 3.58 (s, 2H), 5.00-5.10 (m, 1H), 6.95-7.38 (m, 9H), 8.16-8.24 (m, 1H).

Example 34

Following conventional procedures well known in the pharmaceutical art the following representative pharmaceutical dosage forms containing a compound of formula (I) can be prepared:

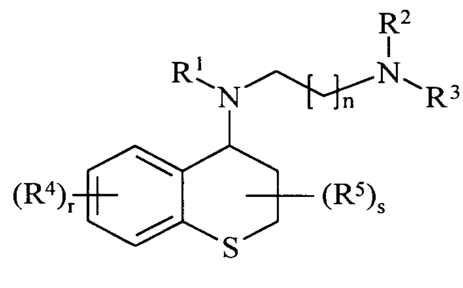
(a)	Tablet	mg/tablet
	Compound of Formula I	50.0
	Mannitol, USP	223.75
	Croscarmellose sodium	60
	Maize starch	15.0
	Hydroxypropylmethylcellulose (HPMC), USP	2.25
	Magnesium stearate	3.0
(b)	Capsule	mg/capsule
	Compound of Formula I	10.0
	Mannitol, USP	488.5
	Croscarmellose sodium	15.0
	Magnesium stearate	1.5

(c) Injection

For intravenous administration, a compound of Formula (I) is dissolved in an isotonic sterile solution (5 mg/mL).

CLAIMS:

1. A method for treating neurological disorders comprising administration of a therapeutically-effective amount of any compound according to formula (I):



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-$(C_{1-6}alkyl)_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-$(C_{1-6}alkyl)_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-$(C_{1-6}alkyl)$amino, *N,N*-$(C_{1-6}alkyl)_2$amino, C_{1-6}alkanoylamino, *N*-$(C_{1-6}alkyl)$carbamoyl, *N,N*-$(C_{1-6}alkyl)_2$carbamoyl, C_{1-6}alkyl$S(O)_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-$(C_{1-6}alkyl)$sulphamoyl, *N,N*-$(C_{1-6}alkyl)_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally

substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl;

R^4 is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the values of R^4 may be the same or different; and

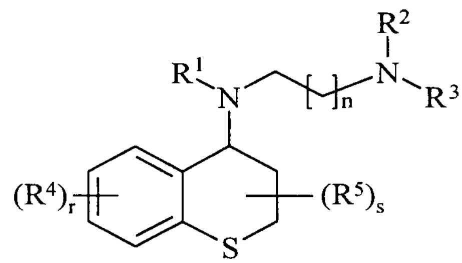
s is 0, 1, 2 or 3 wherein at each occurrence the values of R^5 may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

2. The method according to Claim 1, for treating stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia.

3. The method according to Claim 1, for treating neurological disorders treatable by inhibition of the [^{3}H]-emopamil binding site.

4. A pharmaceutical composition comprising any compound according to formula (I), or a *in vivo*-hydrolysable ester, amide or carbamate thereof, together with a pharmaceutically-acceptable carrier, wherein, in a compound of formula (I):



(I)

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-($C_{1-

${}_{6}$alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl;

R^4 is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the values of R^4 may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the values of R^5 may be the same or different.

5. A pharmaceutical composition according to Claim 4, comprising any compound in accord with formula (I), wherein:

R^1 is hydrogen, C_{1-6}alkyl or C_{2-6}alkenyl;

R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring wherein a heterocyclic ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl;

r is 0;

s is 0; and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

6. A pharmaceutical composition according to Claim 5, comprising any compound in accord with formula (I), wherein:

R^1 is hydrogen, methyl, ethyl or allyl;

R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a piperidin-1-yl, morpholino, 4-methylpiperazin-1-yl, or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

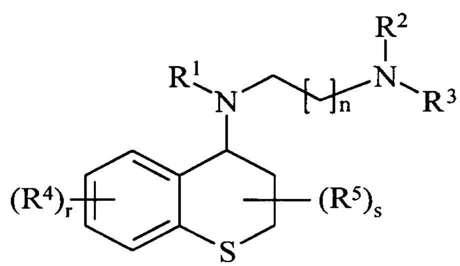
7. A pharmaceutical composition according to Claim 6, comprising any compound in accord with formula (I), wherein:

R^1 is methyl;

R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen to which they are attached in combination form a piperidin-1-yl, morpholino or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

8. Any compound according to formula (I):



(I)

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-$(C_{1-6}alkyl)_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-$(C_{1-6}alkyl)_2$carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12}cycloalkyl and C_{3-12}cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano,

hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl;

R^4 is selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, cyano, nitro or C_{2-6}alkenyl;

R^5 is C_{1-6}alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the values of R^4 may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the values of R^5 may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof;

with a proviso wherein in such compounds:

if R^1 is hydrogen, R^2 and R^3 and the nitrogen to which they are attached in combination form a morpholine or piperidine ring, n is 1 and s is 0, then r is not 0, or R^4 is not a 5-linked ethoxy moiety.

9. A compound according to Claim 8, wherein:

R^1 is hydrogen, C_{1-6}alkyl or C_{2-6}alkenyl;

R^2 and R^3 are independently selected from hydrogen, aryl and C_{1-6}alkyl optionally substituted with aryl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring wherein a heterocyclic ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl;

r is 0;

s is 0; and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

10. A compound according to Claim 9, wherein:

R^1 is hydrogen, methyl, ethyl or allyl;

R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a piperidin-1-yl, morpholino, 4-methylpiperazin-1-yl, or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

11. A compound according to Claim 10, wherein:

R^1 is methyl;

R^2 and R^3 are independently selected from methyl or benzyl, or R^2 and R^3 and the nitrogen to which they are attached in combination form a piperidin-1-yl, morpholino or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

12. A compound according to Claim 8, selected from:

4-(2-(piperidin-1-yl)ethyl(*N*-methyl)amino)thiochroman;

4-(2-(morpholino)ethyl(*N*-methyl)amino)thiochroman;

4-(2-(piperidin-1-yl)ethyl(*N*-ethyl)amino)thiochroman;

4-(2-(morpholino)ethyl(*N*-allyl)amino)thiochroman;

(-)-4-(2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethylamino)thiochroman;

4-(3-morpholin-4-ylpropylamino)thiochroman;

4-(2-dimethylaminoethylamino)thiochroman;

4-(2-isopropylaminoethylamino)thiochroman;

4-((2-pyrrolidin-1-ylethyl)amino)thiochroman;

4-(2-diethylaminoethylamino)thiochroman;

4-((3-piperidin-1-ylpropyl)amino)thiochroman;

4-((3-(4-methylpiperazin-1-yl)propyl)amino)thiochroman;

4-(2-phenylaminoethylamino)thiochroman;

4-(2-benzylaminoethylamino)thiochroman;

4-(methyl-(3-(4-methylpiperazin-1-yl)propyl)amino)thiochroman;

4-(ethyl-(2-morpholin-4-yl-ethyl)amino)thiochroman;

(*R*)-4-(2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl)amino)thiochroman;

(*S*)-4-(*N'*-(2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-*N'*-ethyl)amino)thiochroman;

(*R*)-4-(*N'*-(2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-*N'*-ethyl)amino)thiochroman;

(*S*)-4-(*N*-2-(*N'*-benzyl-*N'*-methylamino)ethyl(*N*-methyl)amino)thiochroman;

(*S*)-4-(*N'*-methyl-*N'*-(2-pyrrolidin-1-ylethyl)amino)thiochroman;

(*S*)-4-(*N'*-(2-(1,3-dihydroisoindol-2-yl)ethyl)-*N'*-methylamino)thiochroman;

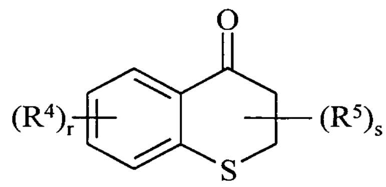
(*S*)-4-(*N'*-(2-(1,3-dihydroisoindol-2-yl)ethyl)amino)thiochroman;

(*S*)-4-((2-azepan-1-ylethyl)amino)thiochroman, and

(*S*)-4-(2-(*N'*-benzyl-*N'*-methylamino)ethylamino)thiochroman.

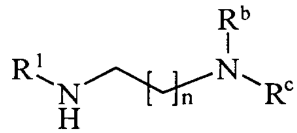
13. A method of making a compound of formula (I) according to Claim 8, wherein R^1, R^2, R^3, R^4, R^5, s, r and n unless otherwise defined are as defined in Claim 8, said method comprising:

a) reacting a ketone of formula (II):



(II)

with an amine of formula (III):

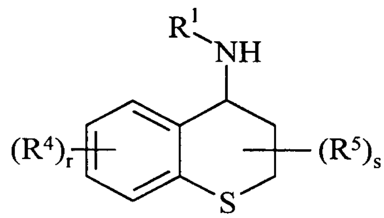


(III);

wherein R^b and R^c are R^2 and R^3 respectively, unless the value of R^2 and/or R^3 is hydrogen, in which case the appropriate R^b and/or R^c is a suitable amino protecting group such as those defined below;

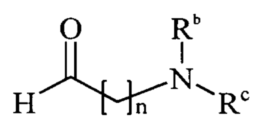
or

b) reacting an amine of formula (IV):



(IV)

with an aldehyde of formula (V):

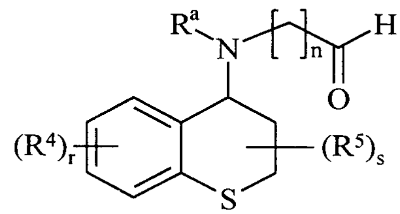


(V)

wherein R^b and R^c are as defined above;

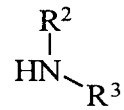
or

c) reacting an aldehyde of formula (VI):



(VI)

with an amine of formula:

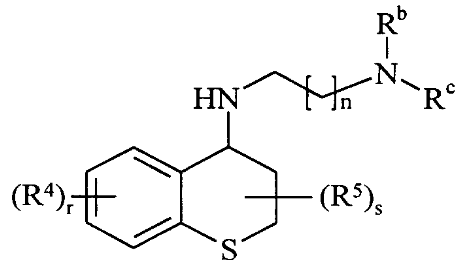


(VII)

wherein R^a is R^1 unless the value of R^1 is hydrogen, in which case R^a is a suitable amino protecting group such as those defined below;

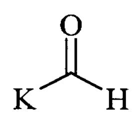
or

d) if R^1 is C_{1-6}alkyl, reacting a compound of formula (VIII):



(VIII)

wherein R^b and R^c are as defined above, with a compound of formula (IX);

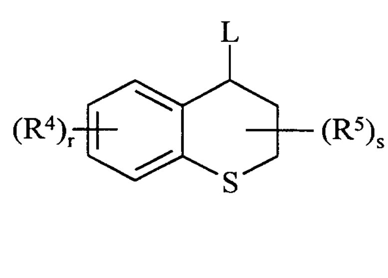


(IX)

wherein K is hydrogen or C_{1-5}alkyl;

or

e) reacting a compound of formula (X):

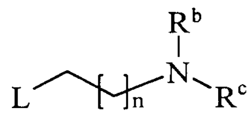


(X)

wherein L is a suitable displaceable group, with an amine of formula (III);

or

f) reacting an amine of formula (IV) with a compound of formula (XI):

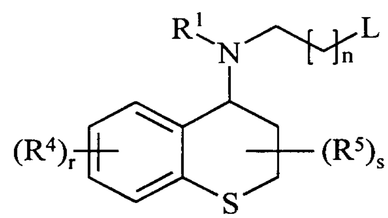


(XI)

wherein L is a suitable displaceable group and R^b and R^c are as defined above;

or

g) reacting a compound of formula (XII):



(XII)

wherein L is a suitable displaceable group, with an amine of formula (VII);

or

h) if R^1 is not hydrogen, reacting a compound of formula (VIII) with a compound of formula (XIII):

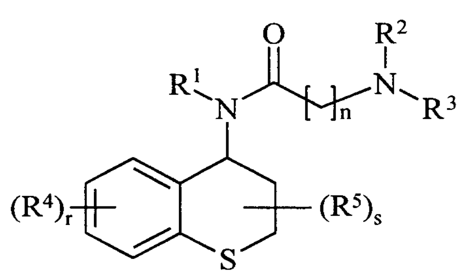
R^1-L

(XIII)

wherein L is a suitable displaceable group;

or

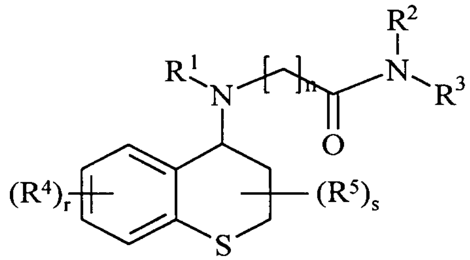
i) reducing a compound of formula (XIV):



(XIV)

or

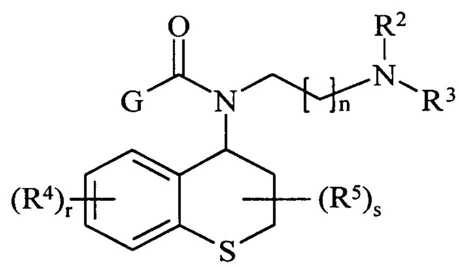
j) reducing a compound of formula (XV):



(XV)

or

k) if R^1 is not hydrogen, reducing a compound of formula (XVI):



(XVI)

wherein:

to prepare a compound wherein R^1 is methyl, G is a suitable displaceable group;

to prepare a compound wherein R^1 is C_{2-6}alkyl, G is C_{1-5}alkyl;

and thereafter if necessary:

converting a compound of the formula (I) into another compound of the formula (I);

removing any protecting groups; and

forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/GB 00/02312

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D335/06 C07D409/12 A61K31/382 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 67, no. 15, 9 October 1967 (1967-10-09) Columbus, Ohio, US; abstract no. 73477, SEN, ANATH B. ET AL: "Potential amebicides. XXIV" XP002152669 abstract & J. INDIAN CHEM. SOC. (1966), 43(7), 521-5 , 1966, ---	8-11
Y	WO 98 00412 A (SCHERING CORP.) 8 January 1998 (1998-01-08) the whole document ---	1,2,4-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2000	30/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beslier, L

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International Application No
PCT/GB 00/02312

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 31887 A (ZENECA LTD.) 4 September 1997 (1997-09-04) the whole document	1,2,4-13
Y	FR 2 687 401 A (LES LABORATOIRES MERAM) 20 August 1993 (1993-08-20) the whole document	1,2,4-13
P,Y	WO 99 38863 A (ZENECA LTD.) 5 August 1999 (1999-08-05) the whole document	1-13
P,Y	WO 00 40574 A (ASTRAZENECA UK LTD.) 13 July 2000 (2000-07-13) the whole document	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02312

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